COST-EFFECTIVENESS OF TESAMORELIN IN THE TREATMENT OF LIPOHYPERTROPHY IN THE US

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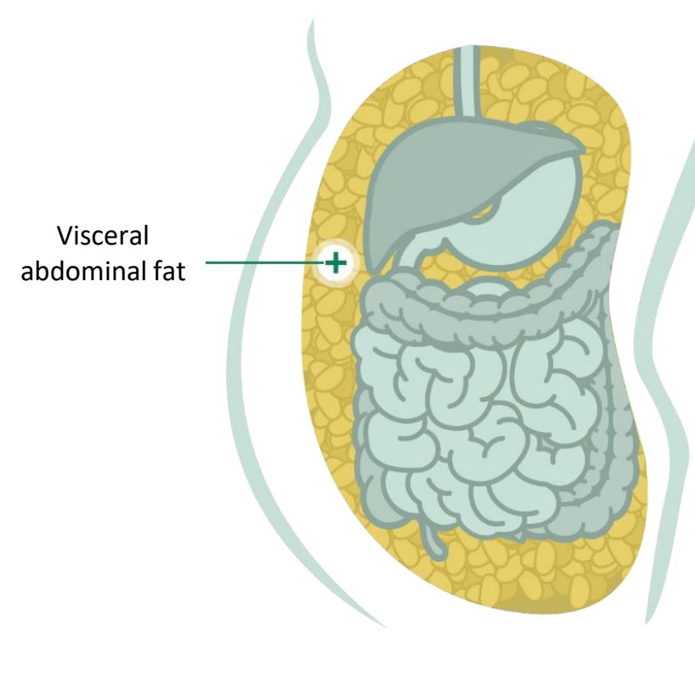
Introduction

HIV-associated Lipohypertrophy

- With advances in treatment over the past few decades, deaths related to acquired immune deficiency syndrome (AIDS) in human immunodeficiency virus (HIV) have steadily decreased. However, because HIV patients are living longer, the virus has more time to affect organ function, leading to an increase in associated comorbidities.(1)
- One such comorbidity is lipohypertrophy, which causes localized abnormal fat accumulation, mostly in the intra-abdominal compartment.(2)



Disease Burden

- HIV-associated lipohypertrophy can be linked to the development of serious metabolic disturbances, including hyperlipidemia, insulin resistance, and hyperglycemia.(3)
- The resulting increase in visceral abdominal fat is linked with an increase in cardiovascular disease (CVD) risk factors, 5-year all-cause mortality, and development of non-alcoholic steatohepatitis (NASH).(4)
- The risk associated with lipohypertrophy is significant and requires treatment to avoid development or progression of metabolic diseases.

Unmet Need and Current Standard of Care

- Data about management of lipohypertrophy with lifestyle changes, eg, diet and exercise are inconsistent.(2)
- Various medications have been investigated for their effects on HIV-associated lipohypertrophy, but other than *EGRIFTA SV*™ (tesamorelin for injection), none have been approved by the FDA for this use.

Tesamorelin for Injection

- In November 2018, tesamorelin (*EGRIFTA SV*™) was approved by the US Food and Drug Administration (FDA) to reduce excess abdominal fat in HIV-infected patients with lipohypertrophy.(5)
- Tesamorelin is a human growth hormone-releasing factor (GHRF) analog. GHRF stimulates the synthesis and physiologic pulsatile release of endogenous growth hormones (GH).

- Tesamorelin has been studied in two phase 3, randomized, placebo-controlled studies (Study LIPO-010 and LIPO-011).(6,7)
- Both studies were conducted in HIV-infected patients with lipohypertrophy, consisting of 26-week randomized main phases and subsequently re-randomized 26-week extension phases.(2,6,7)

Objective: This cost utility analysis of tesamorelin in patients with lipohypertrophy examined the costs and outcomes in terms of quality-adjusted life years (QALYs) from a US private drug plan perspective.

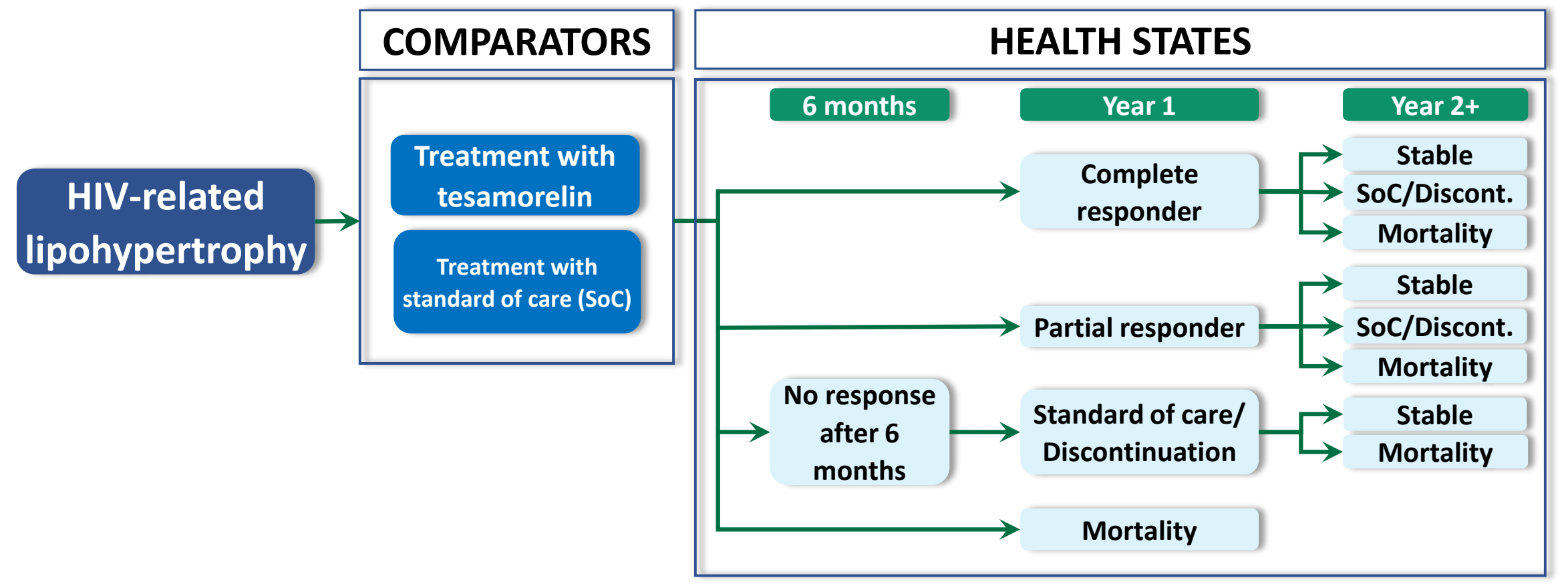
Methods

Model Design and Health States

- This study utilized a hybrid model composed of a decision-tree followed by a long-term Markov model. At treatment initiation, patients either started tesamorelin or standard of care (SoC). Patients discontinued the assigned treatment if no positive response occurred after 6 months. The model assumed that after 1 year, patients fell into one of the following health state categories: complete responder, partial responder, SoC/discontinuation (patient stops receiving tesamorelin and starts treatment with SoC), death.

Technical Assumptions

- For year 2 and beyond, three health states were assumed: stable (patient continues treatment), SoC/discontinuation (discontinuation rate from patient-level clinical data was applied), and death. Patients were assigned to a new health state every year.


COMPARATORS
HEALTH STATES
6 months
Year 1
Year 2+
HIV-related lipohypertrophy
Treatment with tesamorelin
Treatment with standard of care (SoC)
Complete responder
Stable
SoC/Discont.
Mortality
Partial responder
Stable
SoC/Discont.
Mortality
No response after 6 months
Standard of care/ Discontinuation
Stable
Mortality
Mortality

- Regarding included clinical events, three types of health consequences were linked to HIV-associated lipohypertrophy: chronic disease (e.g., diabetes mellitus type 2 [DM2], hypertension, mild cognitive impairment, osteoporosis), acute events (e.g., myocardial infarction, stroke, venous thromboembolism), and HIV treatment non-adherence (linked to HIV transmission, HIV resistance, tuberculosis (TB), hepatitis C virus (HCV), and sepsis).
- Comparators: tesamorelin treatment or SoC, including lifestyle modifications, nutrition, and physical activity.
- Perspective: US private drug plans.
- Costs: all cost data were inflated to 2019 US dollars using the Bureau of Labor Statistics Consumer Price Index for medical care.
- Model population: hypothetical patient population 18 to 65 years of age, with average age in the model at baseline at 45, similar to patients in the tesamorelin clinical trials.
- Time horizon: 30 years. Discount rate: Both costs and benefits were discounted at 3.0% per year.

Model Parameters

Clinical effectiveness

- Complete and partial response rates in the tesamorelin clinical trial were 68.4% and 31.6%, respectively.
- Based on published literature, relative risks for patients with HIV-associated lipohypertrophy vs general healthy population were identified for each clinical event (Table 1).
- **Table 1:** Relative risks of clinical events

Clinical event in lipohypertrophy	Relative risk	SE	Sources
DM2	4.34	0.05	(3)
HTN	2.19	0.04	(8)
MI	1.26	0.07	(9)
Stroke	1.40	0.13	(10)
VTE	1.30	0.66	(11)
MCI	2.05	0.07	(12)
Osteoporosis	2.19	0.79	(13)

DM2: Diabetes mellitus type 2; HCV: Hepatitis C virus; HTN: Hypertension; MCI: Mild cognitive impairment; MI: Myocardial infarction; SE: Standard error; TB: Tuberculosis; VTE: Venous thromboembolism

Methods (cont'd)

Model Parameters

- Relative risk of mortality was assumed as 2.5 for HIV patients with CD4 cell count ≥500 cells/mm³.(14) Natural mortality, based on CDC National Vital Statistics Reports, was used to produce the HIV patient mortality by applying the relative risk in the model.(15)
- The prevalence of lipohypertrophy-related clinical events in complete responders with tesamorelin was obtained from the National Center for Health online data bank and a literature review. The prevalence of events with SoC was derived by multiplying complete responder prevalence by relative risk. Prevalence with tesamorelin was calculated as follows:

  Complete responder prevalence × 68.4% + partial responder prevalence × 31.6%

  Finally, the prevalence of lipohypertrophy-related clinical events in partial responders was taken as the average of SoC and tesamorelin.
- Prevalence rates for TB, HCV, and sepsis were derived from published literature. The non-adherence rate secondary to lipohypertrophy (22.9%) was applied to calculate the final values used in the model.(16)

Utilities

- The incremental utility of responders in the tesamorelin group vs SoC was employed to calculate QALYs gained, due to the difference in treatment response in both groups. Tremblay et al. reported this value as 0.0725 (95%CI, -0.0095; 0.1546).(17)
- **Table 2:** Calculation of incremental utilities (tesamorelin vs. SoC)

	Utility in non-responders (assumed to be SoC utility)		Utility in partial responders	Utility in tesamorelin	Incremental utility EGRIFTA SVTM vs. SoC
	Value	Source	= (Complete Responders utility + SoC utility) / 2	= Complete Responders utility × 68.4% + Partial Responders utility × 31.6%	= Utility in EGRIFTA SV™ – Utility in SoC
DM2	0.737	(18)	0.754	0.766	0.030
HTN	0.747	(18)	0.759	0.768	0.021
MI	0.731	(18)	0.751	0.765	0.034
Stroke	0.719	(18)	0.746	0.763	0.044
VTE	0.734	(18)	0.753	0.766	0.032
MCI	0.662	(19,20)	0.717	0.754	0.093
Osteoporosis	0.754	(18)	0.763	0.769	0.015
HIV transmission	0.736	(17)	0.754	0.766	0.030
1st HIV resistance	0.707	(17)	0.739	0.761	0.055
2nd HIV resistance	0.707	(17)	0.739	0.761	0.055
TB	0.659	(21,22)	0.716	0.754	0.095
HCV	0.460	(23,24)	0.616	0.722	0.263
Sepsis	0.601	(25)	0.686	0.745	0.144

DM2: Diabetes mellitus type 2; HCV: Hepatitis C; HIV: Human immunodeficiency viruses; HTN: Hypertension; MCI: Mild cognitive impairment; MI: Myocardial infarction; TB: Tuberculosis; VTE: Venous thromboembolism

Costs

- Drug costs: The price of tesamorelin was $5,300/box of 60 × 1-mg vials (30-day supply) for an annual cost of $63,600/patient. Since the comparator, SoC, was based on routine exercise, it was assumed to bear no drug cost.
- Acute events costs like stroke were costed using a one-time cost. Low and high-estimated costs were provided for each of these diseases from a review of published literature. According to physician interviews conducted for the validation of this study, a weighted average of these two costs was assumed.
- Chronic disease costs: Considering the nature of chronic diseases, time-dependent health severity states were used to assign severity related costs (mild, moderate, or severe), based on published data.
- HIV treatment non-adherence events (failure to properly receive the full dosage of the HIV drugs) may cause severe health conditions such as increasing the risk of HIV transmission, HIV resistance, TB, HCV, and sepsis. In the base case analysis, costs of HIV transmission and first and second HIV resistance were assumed as zero.

Results

Analysis

Base case cost-utility analysis

- Over a 30-year horizon, the incremental cost and QALYs gained by tesamorelin treatment vs SoC were $46,123 and 0.5920 respectively, which provided an incremental cost effectiveness ratio (ICER) of $77,908/QALY.

Sensitivity analysis

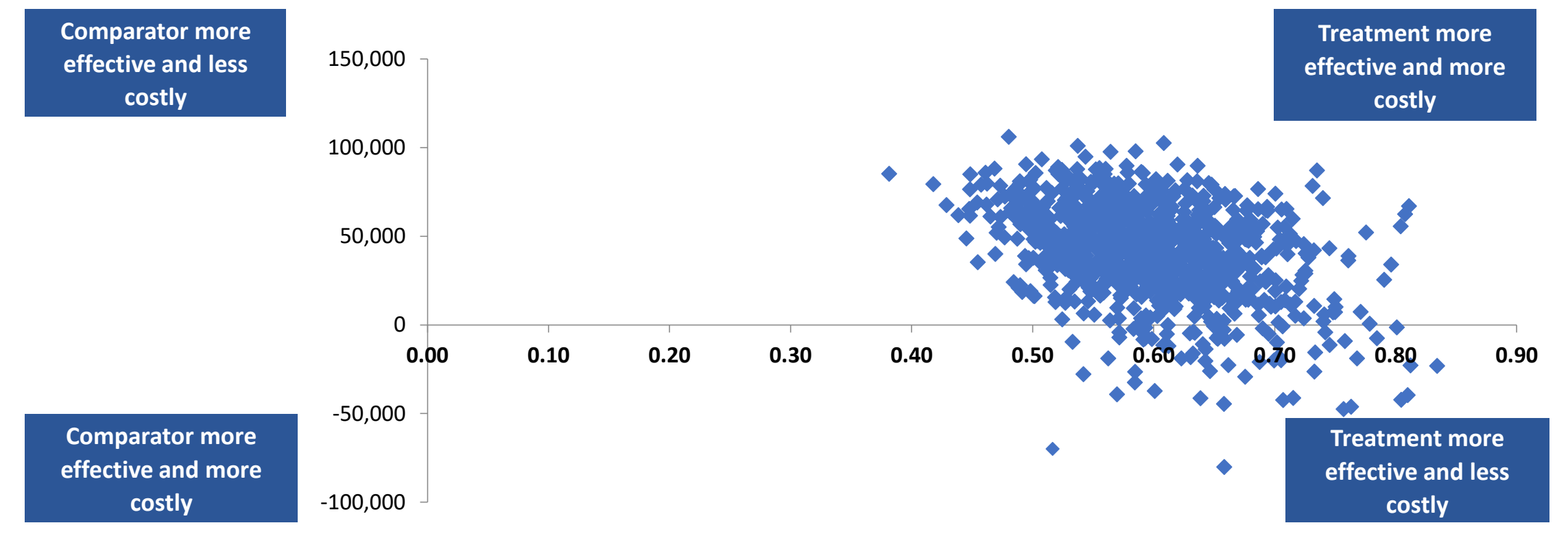
- The results from the tornado diagram were relatively consistent with the base case findings, thereby validating those results. The ICER was most sensitive to variations in the relative risk of osteoporosis, utility of responder, and discontinuation penalty (utility, costs).

Scenario analysis

- By increasing the model's time horizon, the ICER decreased from $166,680/QALY at 10 years to $77,908/QALY at 30 years (base case). The ICER was lower for patients age 20 years than those age 45 years in the base case ($59,858 vs $77,908). Exclusion of discounting (utilities and costs), discontinuation penalty, and mortality decreased the ICER to $38,552, −$83,376, and $54,984, respectively. The base case analysis did not include costs of HIV transmission and resistance. By including these costs, the ICER significantly decreased to −$202,136/QALY.

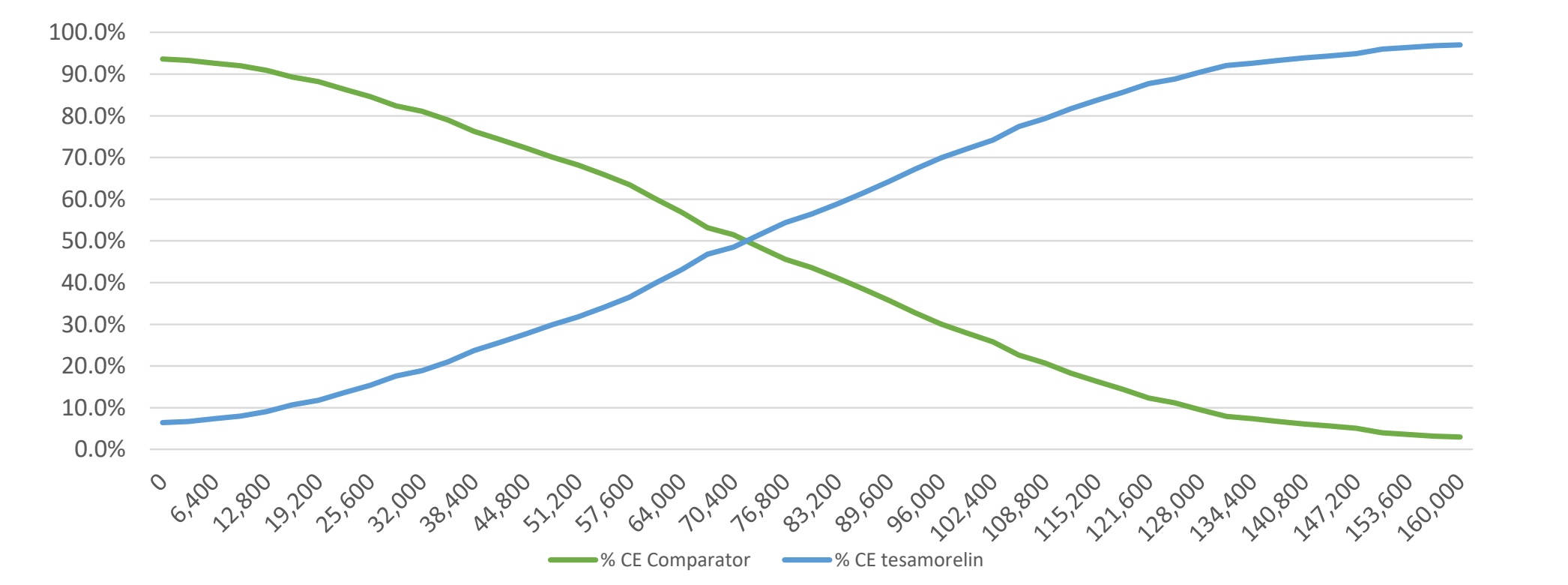
Cost-effectiveness plane

- A cost-effectiveness plane (Figure 3) describes the results of the probabilistic sensitivity analyses (PSAs). Based on this analysis, an average 0.5967 QALYs were gained with tesamorelin vs SoC (95% CI 0.49, 0.72). At an average incremental cost of $41,618 (95% CI −$5,257, $80,037), the resulting average ICER was $69,746 (95% CI −$8,534, $150,293). At willingness-to-pay thresholds of $50,000, $100,000, and $150,000, the probability of tesamorelin being cost effective was 29.5%, 71.8%, and 94.9%, respectively.



Net-benefit approach

- The PSA demonstrated tesamorelin was cost-effective over SoC in most simulations at any threshold >$72,682/QALY.



Discussion

- A cost-utility analysis based on a hybrid model made of a decision tree followed by a long-term Markov model was constructed to estimate the cost-effectiveness of using tesamorelin vs SoC in HIV-associated lipohypertrophy.
- In the model, the clinical efficacy of tesamorelin, which was evaluated in two multicenter double-blind randomized clinical trials, translated into QALYs gained when compared to SoC in the base case analysis.
- Over a 30-year model time horizon, the base case cost-utility analysis found a greater QALY gain (0.59) and a higher overall cost ($46,123) with tesamorelin. The ICER of tesamorelin vs SoC was $77,908/QALY. The three main cost drivers were prevention of DM2, HCV, and osteoporosis. QALY gain was primarily impacted by the utility values of responders, HCV, and DM2.
- Sensitivity analyses were generally consistent with base case findings. The deterministic sensitivity analysis showed the stability of ICER in most input variations, with ICERs being most sensitive to variations in the relative risk of osteoporosis and responder's utility. The PSA found that tesamorelin was a reasonably efficient use of resources, with 71.8% of simulations showing tesamorelin as cost-effective at a $100,000 threshold. The net-benefit approach showed tesamorelin to be cost effective over SoC >50% of the time at any threshold >$72,682. This rate rose to 95% when considering a threshold of $150,293.

Limitations

- The most important limitation is that no clinical study has demonstrated the long-term cardiovascular safety and outcomes of tesamorelin treatment. Each study lasted for 54 weeks, so the response and discontinuation from this trial were used to extrapolate long-term response to treatment and discontinuation. A few assumptions were used to calculate the costs where no data were available, which increases the uncertainty in the results. Another limitation was the source of several utilities used in the model. Some of the utility costs used were based on the broader population and were not specific to patients with HIV-associated lipohypertrophy. In addition, indirect costs (including lost productivity) were not included in the analysis. Since tesamorelin had only minor to moderate adverse events, no adverse event cost was considered.

Conclusion

Tesamorelin is the first FDA-approved drug for the treatment of HIV-associated lipohypertrophy. This cost utility analysis found that incremental cost and QALYs gained by tesamorelin treatment versus SoC were $46,123 and 0.5920, respectively, yielding an ICER of $77,908/QALY. Tesamorelin is an efficacious and cost-effective treatment for lipohypertrophy.

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